Clinical Study Report Synopsis

Drug Substance	AZD5423
Study Code	D2340C00012
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A Phase I, Single-centre, Open, Partly Randomised, Crossover Study in Healthy Subjects to Evaluate AZD5423 Absolute Pulmonary Bioavailability when Administered Inhaled via a New Dry Powder Inhaler, Turbuhaler™, SPIRA Nebuliser, and I-neb® AAD System

Study dates: First subject enrolled: 3 August 2012
Last subject last visit: 4 December 2012

Phase of development: Clinical pharmacology (I)

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Note: Turbuhaler is a trademark of the AstraZeneca group of companies.

Publications

None at the time of writing this report

Objectives and criteria for evaluation

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	Pharmacokinetic	To estimate the $F_{pulmonary}$ of AZD5423 inhaled from the new DPI	$F_{pulmonary}$
Secondary	Pharmacokinetic	To estimate the $F_{pulmonary}$ of AZD5423 inhaled from Turbuhaler™, I-neb®, and SPIRA devices	$F_{pulmonary}$
		To estimate the relative pulmonary and systemic bioavailability between the different devices	Ratios of C_{max} and AUC (not dose normalised) for the comparison of new DPI/Turbuhaler, new DPI/SPIRA, new DPI/I-neb, Turbuhaler/SPIRA, Turbuhaler/I-neb, and SPIRA/I-neb
		To estimate other PK variables of AZD5423 when given intravenously, orally, and inhaled via the new DPI, Turbuhaler, I-neb, and SPIRA devices as single doses	AUC, $AUC_{(0-t)}$, F_{po}, $F_{inhalation,total}$, F_{oral}, C_{max}, t_{max}, $t_{1/2z}$, MAT, MRT, CL, V_z, and V_{ss}
	Safety	To evaluate safety and tolerability following intravenous, oral, and inhaled single doses of AZD5423 via the new DPI, Turbuhaler, I-neb, and SPIRA devices	Adverse events, electrocardiogram, heart rate, blood pressure, pulse rate, body temperature, physical examination, spirometry, laboratory measurements
Exploratory[a]	Pharmacogenetic	To collect and store deoxyribonucleic acid (DNA) for future exploratory research into genes/genetic variation that may influence response (ie, PK, safety, tolerability, and efficacy) to AZD5423 (optional)	-
	Biomarker	To analyse biological samples (eg, human plasma) for circulating biomarkers from consenting volunteers prior to investigational product treatment (optional)	-

Note: Turbuhaler is a trademark of the AstraZeneca group of companies.

a These results, if performed, are not reported in this Clinical Study Report. No biomarker samples were collected in this study.

AUC: area under the plasma concentration-time curve; $AUC_{(0-t)}$: area under the plasma concentration-time curve from zero to the time of the last quantifiable concentration; CL: systemic plasma clearance; C_{max}: maximum plasma concentration; DPI: dry powder inhaler; $F_{inhalation,total}$: absolute bioavailability after inhalation; F_{oral}: oral bioavailability after inhaled treatments; F_{po}: absolute bioavailability after oral administration; $F_{pulmonary}$: absolute pulmonary bioavailability; MAT: mean absorption time; MRT: mean residence time; PK: pharmacokinetic; $t_{1/2}$: terminal half-life; t_{max}: time to maximum plasma concentration; V_{ss}: volume of distribution at steady-state; V_z: volume of distribution at the terminal phase.

Study design

This was an open-label, partly randomised, 6-period, 6-treatment, cross-over single dose study. AZD5423 was administered via the following routes:

- Intravenous infusion (solution)
- Oral administration (suspension)
- Oral inhalation via SPIRA (nebuliser suspension) (Treatment A)
- Oral inhalation via I-neb (nebuliser suspension) (Treatment B)
- Oral inhalation via the new dry powder inhaler (DPI) (dry powder) (Treatment C)
- Oral inhalation via Turbuhaler (dry powder) (Treatment D)

In total, 6 single doses of AZD5423 were administered on 6 separate occasions with a washout period of 14 to 28 days between each treatment. The intravenous infusion was fixed as the 1st treatment (Visit 2, Period 1) and the oral treatment was fixed as the 2nd treatment (Visit 3, Period 2). The healthy volunteers received the 4 oral inhalations (via SIPRA, I-neb, the new DPI, and Turbuhaler) in a randomised order during the last 4 study periods (Visits 4 to 7).

Target subject population and sample size

Healthy male and female (non-childbearing potential) volunteers aged 18 to 45 years (inclusive) with a body mass index (BMI) of 19 to 30 kg/m^2 (inclusive) who provided written informed consent and who were able to inhale the investigational product from the inhaler devices used were to be enrolled in this study.

Planned: 18 healthy volunteers

Screened: 34 healthy volunteers

Randomised: 18 healthy volunteers

Analysed: 18 healthy volunteers

Completed: 16 healthy volunteers

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Table S2 Details of the investigational products

Investigational product	Dosage form and strength	Manufacturer	Batch number
AZD5423 intravenous solution	Solution for infusion, 0.01 mg/mL	AstraZeneca	12-002116AZ
AZD5423 oral suspension	Oral suspension, 0.54 mg/g	AstraZeneca	12-002117AZ
AZD5423 nebulising suspension for SPIRA	Nebuliser suspension, 2.2 mg/g	AstraZeneca	12-002211AZ
AZD5423 nebuliser suspension for I-neb	Nebuliser suspension, 1.6 mg/g	AstraZeneca	12-002210AZ
AZD5423 new dry powder inhaler (DPI)	Inhalation powder, 350 µg/dose[a]	AstraZeneca	12-002779AZ
AZD5423 Turbuhaler	Inhalation powder, 400 µg/dose[a]	AstraZeneca	12-002414AZ

a Strength per dose refers to delivered dose from the new dry powder inhaler and the Turbuhaler.
The actual delivered doses for the SPIRA, I-neb, new DPI, and Turbuhaler treatments were 523, 405, 332, and 514 µg, respectively, instead of the planned 450, 420, 350, and 400 µg.

Duration of treatment

Single dose in 6 periods with a washout period of 14 to 28 days between each treatment

Statistical methods

Pharmacokinetic (PK) variables (AZD5423 plasma concentrations and PK parameters, when applicable) were summarised by treatment and measurement time using appropriate descriptive statistics.

Figures of geometric mean concentration-time data were presented on linear and semi-logarithmic scales by treatment. Figures of individual and geometric mean area under the plasma concentration-time curve from zero to infinity (AUC) and maximum plasma concentration (C_{max}) by treatment were presented.

For the primary objective of absolute pulmonary bioavailability ($F_{pulmonary}$) of AZD5423 inhaled from the new DPI, the geometric mean $F_{pulmonary}$ of AZD5423 inhaled via the new DPI was estimated using an analysis of variance model with log-transformed $F_{pulmonary}$ as the dependent variable and period, sequence and treatment as fixed effects and healthy volunteer within sequence as a random effect. Absolute $F_{pulmonary}$ of AZD5423 inhaled via SPIRA,

I-neb, and Turbuhaler was also estimated from the model. Geometric mean point estimates of $F_{pulmonary}$ were presented for all devices with 90% confidence intervals (CIs).

Ratios of C_{max} and AUC (not dose normalised) were calculated for the comparison of new DPI/Turbuhaler, new DPI/SPIRA, new DPI/I-neb, Turbuhaler/SPIRA, Turbuhaler/I-neb, and SPIRA/I-neb.

All safety data (scheduled and unscheduled) were presented in the data listings. Continuous variables (haematology, clinical chemistry, spirometry, and vital signs) were summarised using descriptive statistics (n, mean, standard deviation [SD], minimum, median, and maximum) by treatment and scheduled time point, as appropriate. Categorical variables (eg, urinalysis) were summarised in frequency tables (frequency and proportion) by treatment and scheduled time point, as appropriate. Where applicable, data were summarised for the observed value at each scheduled assessment, and for the corresponding change from baseline.

Subject population

The age of the healthy volunteers ranged from 21 to 40 years (mean and median 30 years), the BMI from 19.18 to 29.96 kg/m^2 (mean 24.75 kg/m^2 and median 24.84 kg/m^2), and the weight from 66.20 to 94.90 kg, in accordance with the inclusion criteria. All healthy volunteers were male.

Two healthy volunteers (11.1%) were prematurely withdrawn: 1 healthy volunteer due to a positive alcohol screen at admission of Period 5 and 1 healthy volunteer met the stopping criterion of a confirmed isolated total bilirubin increase of >2 times the upper limit of normal (ULN).

Summary of pharmacokinetic results

AZD5423 exposure (C_{max} and AUC) was the highest following intravenous treatment, and lowest following the oral treatment. The systemic exposure following administration via new DPI was 1.53 fold higher compared to I-neb, 0.820 compared to SPIRA, and 1.11 compared to Turbuhaler. The mean CL and V_{ss} following the intravenous treatment were 38.5 L/h and 543 L, respectively. The mean absolute bioavailability of AZD5423 was 4.43% following oral administration. The mean $t_{1/2}$ values were consistent across the 4 inhalation treatments and ranged from 19.7 to 28.9 hours.

The absolute pulmonary bioavailability of AZD5423 inhaled via the new DPI, SPIRA, I-neb, and Turbuhaler device was approximately 42.5%, 33.7%, 21.1%, and 24.8%, respectively, with the actual delivered dose at 332, 523, 405, and 514 µg.

Summary of safety results

No deaths, serious adverse events (SAEs), or discontinuations due to an adverse event (AE) were reported. Overall, at least 1 AE was reported for 11 healthy volunteers (61.1%) with the highest incidence of healthy volunteers with at least 1 AE was reported after the oral treatment.

Overall, the most frequently reported AE was headache, reported after the intravenous, oral, SPIRA, and I-neb treatments. No pattern was observed between the treatments in the number, relationship, and severity of AEs reported.

Laboratory changes outside the predefined criteria were reported, but none were reported as AEs. None of the out of range values was considered to be of clinical significance by the Investigator. No safety concerns were identified based on AEs, laboratory measurements, vital signs, spirometry, electrocardiogram (ECG), or physical examination findings.